Why and when PCI, why and when thrombolysis?

Thrombolysis

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Several reasons support the use of thrombolysis (TBL) in the treatment of patients with ST-segment elevation myocardial infarction (STEMI).

1. **TBL is easy to provide** TBL can be delivered as a pre-hospital bolus by a paramedic after electrocardiographic confirmation and after filling-in a very simple inclusion–exclusion form. This can be performed virtually everywhere: at home, across rural sites, on a ship, but also in a busy metropolitan area jammed by traffic or by snow or by whatever makes the anticipated time to inflate the balloon to exceed 90 min [1]. These items are those typically affecting countries like Italy, where geographic and logistic barriers are well recognized.

2. **Primary angioplasty (P-PCI) is inherently complicated** P-PCI requires the immediate availability of a shuttle to take the patient to the nearest cath-lab in a timely fashion. There is unequivocal evidence that time is a critical issue for P-PCI. It encompasses the time to wait for the shuttle, for getting into and out of the shuttle, the transportation time and the time required at arrival for getting the balloon inflated. These components of the time-delay from first contact to balloon inflation (D2B time) can only be predicted roughly and in the real world, the prediction is usually optimistic, compared to the final result. In the United States, the median D2B time has recently improved to 82’, but the balloon is inflated within 90’ only in 59% of patients [2], thus missing the 75% D2B Alliance campaign minimal goal. In Italy, at best, the D2B time is said to be 71’ for in-site and 112’ for transferred patients [3]. Furthermore, the “huge” effort required to reduce the D2B time (85’ to 74’ for in site and 165’ to 128’ for transferred patients) did not result in a mortality benefit [4] in the RACE registry.

3. **P-PCI cannot be facilitated** The effort to extend the D2B time beyond 90’ by injecting a drug before P-PCI so far has been unsuccessful [5] and it also increases the risk of bleeding. For this very reason, someone advocates the increase in the number of catheterization laboratories [6]. However, this proliferation has its drawbacks on its own. First, it decreases the center and operator activity volume, a primary determinant of quality and mortality yield [7]. Second, the opening of new catheterization facilities will increase population-based rates of coronary revascularization, particularly among patients without myocardial infarction [8], with the obvious risk of increasing the number of non-appropriate catheterization procedures [9], not to say the costs. Can the society afford such a burden, without any scientific proof of efficacy?

4. **TBL can be greatly facilitated** In the last few years, it has been shown that the results of TBL can be facilitated in several ways. First and probably, the most important is the development of efficient territorial networks. Again, in Italy, it is now estimated that 50–60% of STEMI patients are recognized by the emergency system in the first 2–3 h after the onset of symptoms. At this time, coronary thrombus is small, fresh and easily amenable to lysis. P-PCI has very little to offer more than TBL in this framework. Second, the results of TBL can be improved (in terms of recurrent ischemia, even if not of mortality) by subsequent angioplasty, provided that at least 4 h are allowed to

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elapse after TBL to avoid the injury to the vessel wall in a lytic state (risk of intra-plaque hemorrhage) [10, 11]. Third, the double anti-platelet regimen with aspirin and clopidogrel after TBL decreases coronary occlusion, clinical re-infarction and mortality as well [12, 13]. A further improvement may be achieved by adjunctive enoxaparin [14]. From this standpoint, it is clear that this “New Thrombolysis” is in no way comparable to the “Old Thrombolysis” (infusion in-hospital of ancient regimens including plain streptokinase and aspirin).

5. So far, P-PCI has not been shown to reduce total mortality compared to TBL in clinical trials The only evidence for the claim that P-PCI reduces mortality compared to TBL comes from a small, flawed overview of small trials [15]. In fact, no single trial, including the largest DANAMI-2 trial, has been either sized or shown to reduce total mortality using P-PCI. The overview, often incorrectly quoted as “meta-analysis”, only suggests that P-PCI could decrease mortality but needs confirmation in a large, properly planned and sized trial. Too many times have we observed the failure of these flawed “meta-analyses” to predict the efficacy in a following adequate trial. Examples are abundant in the literature: the failure of positive meta-analyses to predict the efficacy of nitrates and magnesium in acute myocardial infarction, or the efficacy of angiotensin-II blockers to prevent atrial fibrillation, or the efficacy of aspirin to prevent eclampsia.

6. Results in trials as opposed to results in registries Registries should not be taken as a proof of efficacy; rather they are supposed to check if a treatment effective in trials is still working when it passes in general use. In the Swedish RIKS-HIA registry, a mortality reduction was observed in the P-PCI group, compared to the TBL group [16]. However, patients who were sent to the cath-lab for STEMI, but did not receive P-PCI for any reason, were excluded. In addition, the multivariable analysis did not include in the propensity score important variables such as the blood pressure, the heart rate, the electrocardiographic site of infarction and the actual amount of ST-segment elevation in the two groups. Furthermore, this registry might suffer from the same selection problems affecting another Swedish registry claiming that drug-eluting stents are dangerous and then 6 months later that they are safe. It should also be recognized that Scandinavian organization standards could not be taken as granted elsewhere. Italian registries, for example, have shown the same mortality rate for P-PCI and TBL (Table 1). The more recent PRIMA-RER registry revealed a similar 6.9% mortality rate after P-PCI [3]. Finally, registries, due to their voluntary nature, still do not reflect the broader population of the real world [17] for which the relative efficacy of P-PCI compared to TBL is totally unknown.

7. The re-infarction issue The only documented benefit of P-PCI is the reduction of re-infarction rate. However, it might be asked why re-infarction prevention does not affect mortality. The answer is unknown, but it might be speculated that native thrombosis is less dangerous than stent thrombosis [18], because both the thrombotic burden is higher in stent thrombosis and the collateral circulation is more developed in native thrombosis. In addition, it is difficult to diagnose a true re-infarction in the first 24 h after TBL, based mainly on ST-segment fluctuations, usually transient in approximately 75% of cases.

Conclusions: a thrombolytic-based strategy is the backbone of STEMI management While we acknowledge that P-PCI is the “preferred” STEMI treatment by European and American guidelines, it is clear that the restructuring of the healthcare system to provide universal P-PCI is not evidence-based. Formidable geographic and logistic barriers do not allow for any automatic translation to the real world of the small (if any) advantages of P-PCI observed in trials.

### Table 1 Mortality rate, according to reperfusion strategy, in Italian STEMI registries

<table>
<thead>
<tr>
<th>Registry</th>
<th>Patients</th>
<th>P-PCI (%)</th>
<th>TBL (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLITZ-1</td>
<td>828</td>
<td>6.5</td>
<td>6.4</td>
<td>NS</td>
</tr>
<tr>
<td>MISTRAL</td>
<td>1,811</td>
<td>8.5</td>
<td>7.2</td>
<td>NS</td>
</tr>
<tr>
<td>VENERE</td>
<td>819</td>
<td>6.6</td>
<td>6.9</td>
<td>NS</td>
</tr>
<tr>
<td>GESTIMA</td>
<td>453</td>
<td>4.6</td>
<td>7.3</td>
<td>NS</td>
</tr>
<tr>
<td>PRIMA</td>
<td>587</td>
<td>7.2</td>
<td>5.9</td>
<td>NS</td>
</tr>
<tr>
<td>Total</td>
<td>4,498</td>
<td>7.0</td>
<td>6.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Fig. 1 FAST-MI: French patients treated with pre-hospital TBL fare well compared to those treated with P-PCI, despite a similar GRACE score (Danchin, European Society of Cardiology Annual Meeting, 2007)
At the same time, it should be recognized that a new excellent option exists: pre-hospital TBL in the first 3 h, with double anti-platelet and enoxaparin treatment and with rescue or clinically driven coronary angiography. This much simpler strategy results in mortality rates of about 6–7%, absolutely competitive with those observed with P-PCI and is now quickly embraced by many western countries (Fig. 1), including North America. Therefore, every effort should be made to gather as many patients as possible within this time-window, to provide this very simple and effective therapy.

References